Claims

1. A crystal of phosphorylated human Aurora-A kinase fragment comprising amino acid residues 122-403 complexed with amino acid residues 1-43 of human TPX2, wherein said crystal diffracts to at least 3 angstrom resolution and has a crystal stability within 5% of its unit cell dimensions.

2. The crystal according to claim 1, having the coordinates as listed in Table B.

3. The crystal according to claim 1 or 2, said crystal belonging to the orthorhombic space group $P2_12_12_1$ and having the unit cell dimensions in angstroms: a = 59.63 ± 5%, b = 81.72 ± 5%, c = 83,05 ± 5%.

4. The crystal according to any one of claims 1 to 3, having a Aurora-A ligand binding site defined by the structure coordinates of Aurora-A amino acids Q127, W128, R126, L159, F157, E170, L169, V206, Y199, H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 according to Table B.

5. A molecule or molecular complexe comprising at least a part of the ligand binding site defined by structure coordinates of Aurora-A amino acids Q127, W128, R126, L159, F157, E170, L169, V206, Y199, H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 according to Table B, or a mutant or homologue thereof.

6. A machine-readable data storage medium comprising a data storage material encoded with machine readable data, wherein the data is defined by the structure coordinates of phosphorylated human Aurora-A kinase complexed with amino acid residues 1-43 of human TPX2 according to Table B or a homologue of said complex, wherein said homologue comprises backbone atoms that have a root mean square deviation from the backbone atoms of the complex of not more than 3.0 A.

7. A binding site in Aurora-A, or a homologue or mutant thereof, for an AR modulator in which a portion of said ligand is in van der Walls contact or hydrogen bonding contact with any portion or all of residues Q127, W128, R126, L159, F157, E170, L169, V206, Y199, H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 of Aurora-A according toTable B.

8. The binding site according to claim 7, wherein the homologue or mutant has 25%-95% identity to residues Q127, W128, R126, L159, F157, E170, L169, V206, Y199,

H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 of Aurora-A according to Table B.

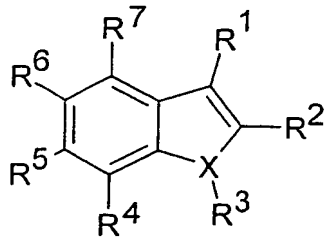
9. A method for identifying a compound that modulates Aurora-A kinase activity, the method comprising any combination of steps of :
a) modeling test compounds that fit spatially into the Aurora-A binding site as defined by structure coordinates according to Table B;
b) using said structure coordinates or binding site as set forth in claim 7 to identify structural and chemical features;
c) employing identified structural or chemical features to design or select compounds as potential Aurora-A modulators;
d) employing the three-dimensional structural model or the ligand binding site to design or select compounds as potential Aurora-A modulators;
e) synthesizing the potential Aurora-A modulators;
f) screening the potential Aurora-A modulators in an assay characterized by binding of a test compound to the Aurora-A; and
g) modifying or replacing one or more amino acids from Aurora-A selected from the group consisting of Q127, W128, R126, L159, F157, E170, L169, V206, Y199, H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 of Aurora-A according to Table B.

10. An Aurora-A modulator identified by the method of claim 9.

11. An allosteric inhibitor of Aurora-A, at least a portion of which binds with any portion or all of residues Q127, W128, R126, L159, F157, E170, L169, V206, Y199, H187, R179, L178, V182, Y199, L188, I184, V252, K250, P282, H280 of Aurora-A according to Table B.

12. The allosteric inhibitor of claim 11, wherein binding is van der Walls contact or hydrogen bonding contact.

13. Indole and indene derivatives of formula (I)



(I)

wherein

R^1 represents hydrogen, alkylene-COR^{11}, alkylene-NHR^8, alkylene-OR^8, or alkylene-SR^8;

R^2 represents hydrogen, alkylene-COR^{11}, alkylene-NHR^8, alkylene-OR^8, or alkylene-SR^8;

R^3 represents hydrogen, alkyl, alkylene-R^9, alkenylene-R^9, alkynylene-R^9, or arylene-R^9;

R^4 represents hydrogen;

R^5 represents hydrogen, alkyl, OR^{10}, NHR^{10}, SR^{10}, alkylene-R^{10}, alkenylene-R^{10}, alkynylene-R^{10}, or arylene-R^{10};

R^6 represents hydrogen, alkyl, OR^{10}, NHR^{10}, SR^{10}, alkylene-R^{10}, alkenylene-R^{10}, alkynylene-R^{10}, or arylene-R^{10};

R^7 represents hydrogen;

R^8 represents hydrogen, CO-alkyl, $(aa)_m asp(aa)_n$, $(aa)_m glu(aa)_n$, or $(aa)_m cys(aa)_n$, or optionally substituted alkyl, aryl or heteroaryl;

R^9 represents NH-alkyl, $N(alkyl)_2$, $N^+(alkyl)_3$, optionally substituted aryl, or optionally substituted heteroaryl;

R^{10} represents hydrogen or a mono- or bicyclic, saturated, partially unsaturated or aromatic, alicyclic or heterocyclic radical which may be substituted;

R^{11} represents hydrogen, alkyl or haloalkyl.

X represents a nitrogen atom or CH;

aa represents an amino acid radical; and

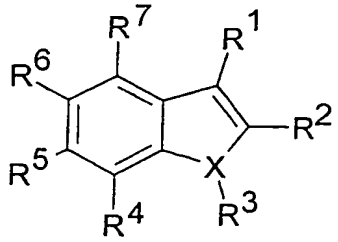
n is zero or an integer of 1 to 10;

m is zero or an integer of 1 to 10,

provided that R^1 and R^2 are not both hydrogen and that R^5 and R^6 are not both hydrogen,

and optical isomers, physiologically acceptable salts, derivatives and prodrugs thereof.

14. Indole and indene derivatives of formula (I)



(I)

wherein

R^1 represents hydrogen, alkylene-NHR^8, alkylene-OR^8, or alkylene-SR^8;

R^2 represents hydrogen, alkylene-NHR^8, alkylene-OR^8, or alkylene-SR^8;

R^3 represents hydrogen, alkyl, alkylene-R^9, alkenylene-R^9, alkynylene-R^9, or arylene-R^9;

R^4 represents hydrogen;

R^5 represents hydrogen, alkyl, OR^{10}, NHR^{10}, SR^{10}, alkylene-R^{10}, alkenylene-R^{10}, alkynylene-R^{10}, or arylene-R^{10};

R^6 represents hydrogen, alkyl, OR^{10}, NHR^{10}, SR^{10}, alkylene-R^{10}, alkenylene-R^{10}, alkynylene-R^{10}, or arylene-R^{10};

R^7 represents hydrogen;

R^8 represents hydrogen, CO-alkyl, $(aa)_m asp(aa)_n$, $(aa)_m glu(aa)_n$, or $(aa)_m cys(aa)_n$;

R^9 represents NH-alkyl, $N(alkyl)_2$, $N^+(alkyl)_3$, aryl, or heteroaryl;

R^{10} represents hydrogen, aryl, or substituted aryl;

X represents a nitrogen atom or CH;

aa represents an amino acid radical; and

n is zero or an integer of 1 to 10;

m is zero or an integer of 1 to 10,

provided that R^1 and R^2 are not both hydrogen and that R^5 and R^6 are not both hydrogen,

and optical isomers, physiologically acceptable salts and prodrugs thereof.

15. The compound according to claim 13 or 14, wherein one of residues R^1 and R^2, preferably R^2, is hydrogen and the other, preferably R^1, represents alkylene-NHR^8.

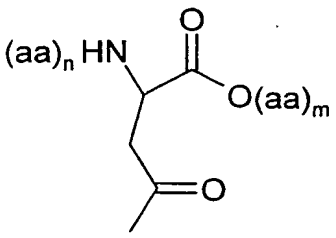
16. The compound according to claim 13 or 14, wherein one of residues R^1 and R^2, preferably R^2, is hydrogen and the other, preferably R^1, represents alkylene-OR^8.

17. The compound according to claim 16, wherein R^8 is hydrogen.

18. The compound according to claim 13 or 14, wherein one of residues R^1 and R^2, preferably R^2, is hydrogen and the other, preferably R^1, represents alkylene-COR^{11}.

19. The compound according to claim 18, wherein R^{11} is hydrogen, methyl or trifluormethyl.

20. The compound according to claim 13 or 14, wherein R^8 is a radical of the formula (II)



(II)

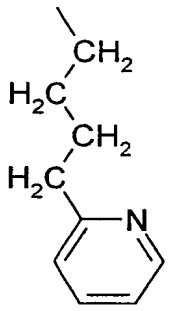
wherein

aa represents an amino acid radical;

n is zero or an integer of 1 to 10; and

m is zero or an integer of 1 to 10.

21. The compound according to any one of claims 13 to 20, wherein R^3 is a radical of the formula (IV)



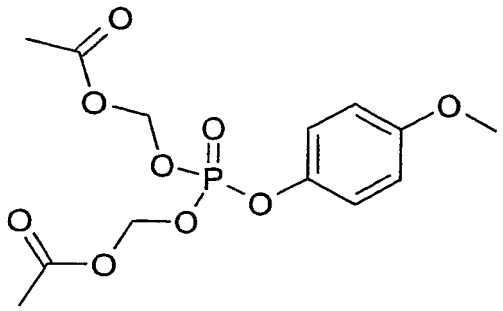
(IV)

22. The compound according to any one of claims 13 to 21, wherein R^5 and/or R^6 represent OR^{10}, wherein R^{10} is defined as in claim 13 or 14.

23. The compound according to any one of claims 13 to 22, wherein R^{10} is aryl which may be substituted with 1, 2 or 3 substituents independently selected from the group consisting of hydroxy $-OPO_3H_2$, $-CH_2PO_3H_2$, $-CF_2PO_3H_2$, -COOH, $-CH(COOH)_2$, $-OPO_3(R^{11})_2$, $-CH_2OPO_3(R^{11})_2$, $-CF_2PO_3(R^{11})_2$, $-COOR^{11}$, and $-CH(COOR^{11})_2$, wherein R^{11} is a radical that is cleavable *in vivo*.

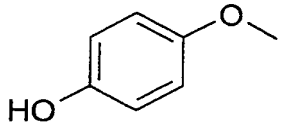
24. The compound according to claim 23, wherein R^{11} represents alkyl, CH_2OCO-alkyl, and C_2H_4-S-CO-alkyl.

25. The compound according to any one of claims 23 or 24, wherein R^5 and/or R^6 are/is the radical of formula (V)



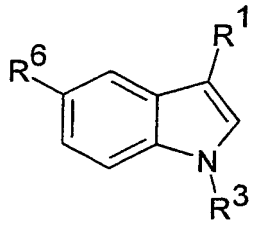
(V)

26. The compound according to claim 23, wherein wherein R^5 and/or R^6 are/is the radical of formula (VI)



(VI)

27. The compound according to claim 13 or 14, having the formula (Ia)

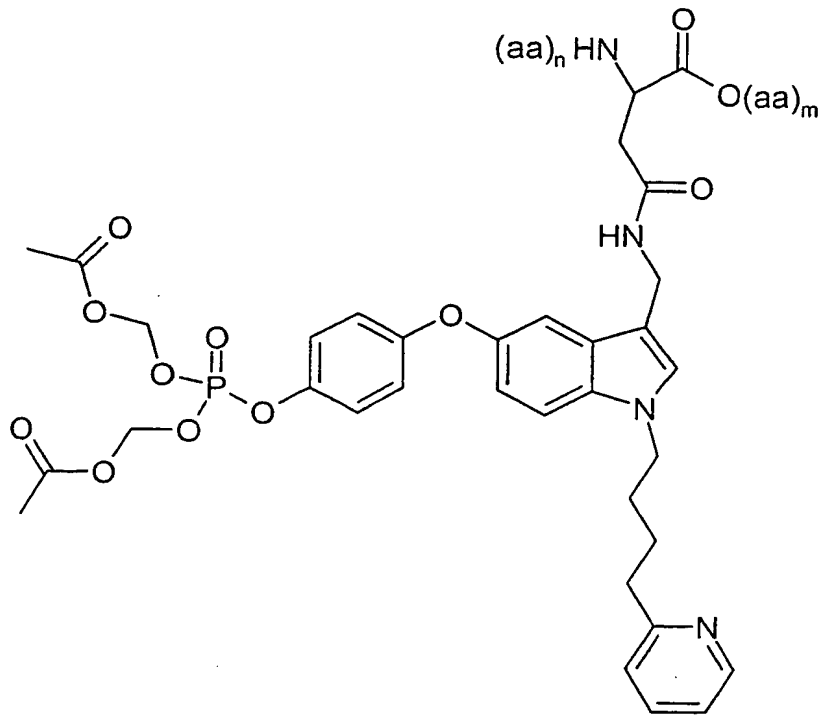


(Ia)

wherein

R^1, R^3 and R^6 are defined as in any one of claims 13 to 26.

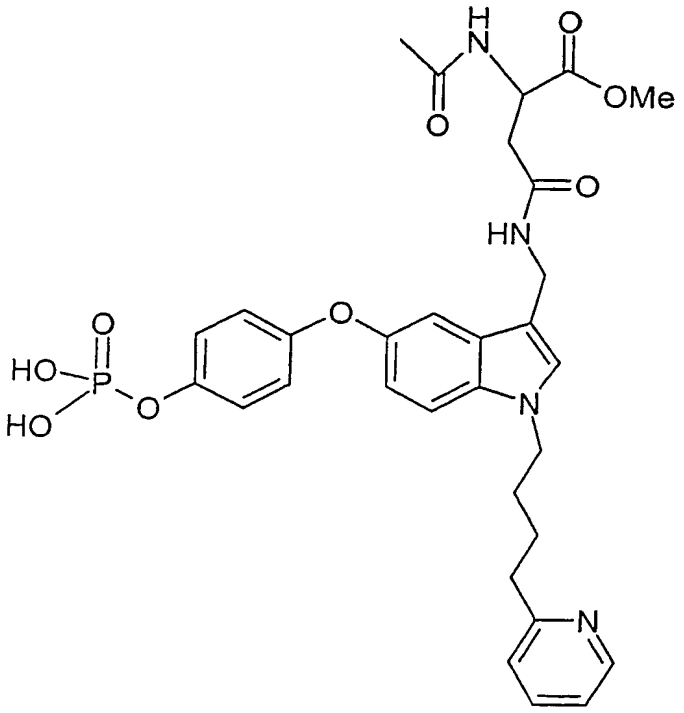
28. The indole derivative of formula (15)



15

wherein
aa, n and m are defined as in claim 13 or 14,
and optical isomers and physiologically acceptable salts thereof.

29. The indole derivative of formula (14)



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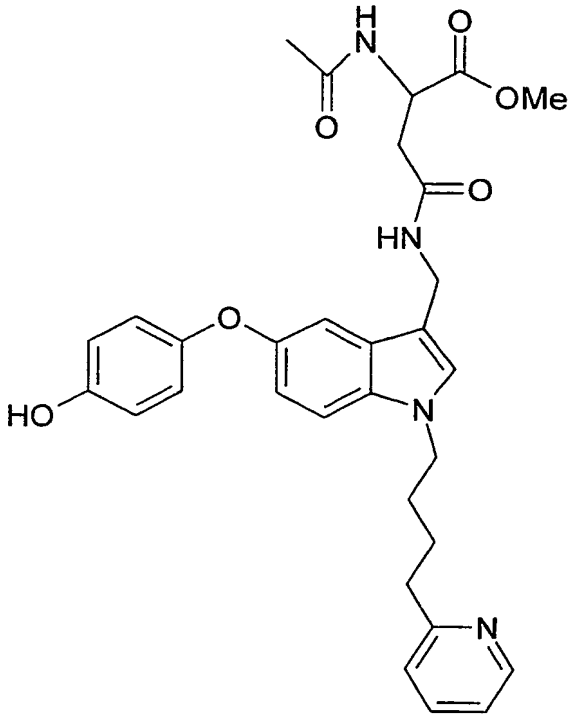
30. The indole derivative of formula (12)



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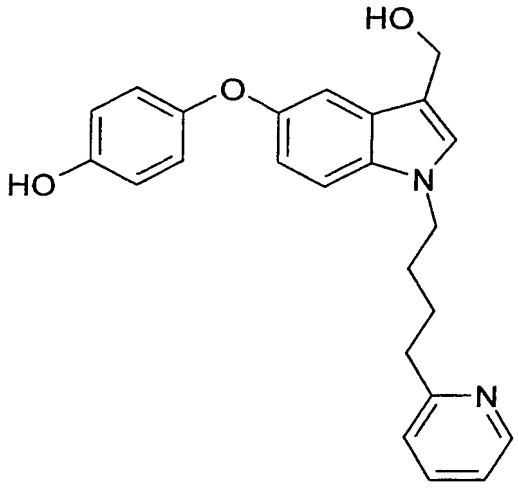
31. The indole derivative of formula (7)



7

32. The Aurora-A modulator of claim 10, the allosteric inhibitor of claims 11 or 12, or the indole or indene derivative of any one of claims 13 to 31 for use in therapy.

33. Pharmaceutical composition, comprising at least one Aurora-A modulator of claim 10, at least one allosteric inhibitor of claims 11 or 12, or at least one indole or indene derivative of any one of claims 13 to 31, optionally in combination with a pharmaceutically acceptable excipient.

34. The use of an Aurora-A modulator of claim 10, of an allosteric inhibitor of claims 11 or 12, or of an indole or indene derivative of any one of claims 13 to 31 in the manufacture of a medicament for treating cancer.

35. The use according to claim 34, wherein the cancer is a breast or colon carcinoma.